

WHAT IS CLAIMED IS:

1. A method of treating a disease mediated by p38 within a host, said method comprising administering to said host a compound of Formula I:



or a pharmaceutically acceptable salt thereof, wherein

D is $-\text{NH}-\text{C}(\text{O})-\text{NH}-$,

A is a substituted or unsubstituted pyridyl, quinoliny or isoquinoliny group,

B is a substituted or unsubstituted, up to tricyclic aryl or heteroaryl moiety of up to 50 carbon atoms with a cyclic structure bound directly to D, containing at least 5 cyclic members with 0-4 members of groups consisting of nitrogen, oxygen and sulfur,

wherein the substituents for A are selected from the group consisting of halogen, up to per-halo, and W_n , where n is 0-3 and each W is independently selected from the group consisting of

C_{1-10} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkyl having at least a five cyclic members and 0-3 heteroatoms selected from N, S and O; C_{2-10} alkenyl, C_{1-10} alkenoyl, C_6-C_{14} aryl, C_7-C_{24} alkaryl, C_7-C_{24} aralkyl, C_3-C_{12} heteroaryl having at least 5 cyclic members and 1-3 heteroatoms selected from O, N and S, C_4-C_{24} alkheteroaryl having at least 5 cyclic members and 1-3 heteroatoms selected from O, N and S;

substituted C_{1-10} alkyl, substituted C_{1-10} alkoxy, substituted C_{3-10} cycloalkyl having at least 5 cyclic members and 0-3 heteroatoms selected from N, S and O; substituted C_{2-10} alkenyl, substituted C_{1-10} alkenoyl, substituted C_6-C_{14} aryl, substituted C_7-C_{24} alkaryl, substituted C_7-C_{24} aralkyl, substituted C_3-C_{12} heteroaryl having at least 5 members and 1-3 heteratoms selected from O, N and S, substituted C_4-C_{24} alkheteroaryl having at least 5 members and 1-3 heteroatoms selected from O, N and S,

$-\text{CN}$, $-\text{CO}_2\text{R}^7$, $-\text{C}(\text{O})\text{NR}^7\text{R}^{7'}$, $-\text{C}(\text{O})-\text{R}^7$, $-\text{NO}_2$, $-\text{OR}^7$, $-\text{SR}^7$, $-\text{NR}^7\text{R}^{7'}$, $-\text{NR}^7\text{C}(\text{O})\text{OR}^{7'}$, $-\text{NR}^7\text{C}(\text{O})\text{R}^{7'}$, with each R^7 and $\text{R}^{7'}$ independently selected from

hydrogen, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, C₂₋₁₀ alkenyl, C₁₋₁₀ alkenoyl, up to per halosubstituted C₁₋₁₀ alkyl, up to per halosubstituted C₁₋₁₀ alkoxy, up to per halosubstituted C₂₋₁₀ alkenyl and up to per halosubstituted C₁₋₁₀ alkenoyl, C₃₋₁₀ cycloalkyl having at least 5 cyclic members and 0-3 heteroatoms selected from O, S and N, C₆₋₁₄ aryl, C₃₋₁₀ hetaryl having at least 6 cyclic members and 0-3 heteroatoms selected from O, S and N, up to per halo substituted C₃₋₁₀ cycloalkyl having at least 5 cyclic members and 0-3 heteroatoms selected from O, S and N, up to per halo substituted C₆₋₁₄ aryl and up to per halo substituted C₃₋₁₀ hetaryl having at least 6 cyclic members and 0-3 heteroatoms selected from O, S and N,

where W is a substituted group, it is substituted by halogen, up to per halo, or by one or more substituents independently selected from the group consisting of -CN, -CO₂R⁷, -C(O)NR⁷R^{7'}, -C(O)-R⁷, -NO₂, -OR⁷, -SR⁷, -NR⁷R^{7'}, -NR⁷C(O)OR^{7'}, and -NR⁷C(O)R^{7'}, wherein R⁷ and R^{7'} are independently as defined above;

wherein the substituents for B are selected from the group consisting of halogen, up to per-halo, and J_n, where n is 0-3 and each J is independently selected from the group consisting of -CN, -CO₂R⁷, -C(O)NR⁷R^{7'}, -C(O)-R⁷, -NO₂, -OR⁷, -SR⁷, -NR⁷R^{7'}, -NR⁷C(O)OR^{7'}, -NR⁷C(O)R^{7'}, with each R⁷ and R^{7'} independently as defined for W above, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkyl having at least five cyclic members and 0-3 heteroatoms, C₂₋₁₀ alkenyl, C₁₋₁₀ alkenoyl, C₆₋₁₄ aryl, C₃₋₁₂ hetaryl having at least a five cyclic members and 1-3 heteroatoms selected from N, S and O, C₇₋₂₄ aralkyl, C₇₋₂₄ alkaryl, C₄₋₂₃ alkyheteroaryl having at least six members and 1-3 heteroatoms selected from O, N and S, substituted C₁₋₁₀ alkyl, substituted C₁₋₁₀ alkoxy, substituted C₃₋₁₀ cycloalkyl having at least a five-members and 0-3 heteroatoms selected from N, S and O, substituted C₂₋₁₀ alkenyl, substituted C₁₋₁₀ alkenoyl, substituted C₆₋₁₄ aryl, substituted C₃₋₁₂ hetaryl having at least five cyclic members and 1-3 heteroatoms selected from N, S and O, substituted C₇₋₂₄ alkaryl, substituted C₇₋₂₄ aralkyl and substituted C₄₋₂₃ alkyheteroaryl having at least six members and 1-3 heteroatoms selected from O, N and S, and -Q-Ar,

wherein Q is a single bond, -O-, -S-, -N(R⁷)-, -(CH₂)_m-, -C(O)-, -CH(OH)-, -(CH₂)_mO-, -(CH₂)_mS-, -(CH₂)_mN(R⁷)-, -O(CH₂)_m-CHX^a-, -CX^a₂-, -S-(CH₂)_m- and -N(R⁷)(CH₂)_m-, wherein m=1-3, and X^a is halogen; and

Ar is a 5- or 6-member aromatic structure containing 0-2 members selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by halogen, up to per-halo, and optionally substituted by Z_{n1}, wherein n1 is 0 to 3 and each Z is independently selected from the group consisting of -CN, -CO₂R⁷, -COR⁷, -C(O)NR⁷R^{7'}, -OR⁷, -SR⁷, -NO₂, -NR⁷R^{7'}, -NR⁷C(O)R^{7'}, and -NR⁷C(O)OR⁷, with R⁷ and R^{7'} as defined above for W, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, C₂₋₁₀ alkenyl and C₁₋₁₀ alkenoyl, halo substituted C₁₋₁₀ alkyl up to per halo, halo substituted C₁₋₁₀ alkoxy up to per halo, halosubstituted C₂₋₁₀ alkenyl up to per halo and halosubstituted C₁₋₁₀ alkenoyl up to per halo, and

where J is a substituted group, it is substituted by halogen, up to per halo, or by one or more substituents independently selected from the group consisting of -CN, -CO₂R⁷, -COR⁷, -C(O)NR⁷R^{7'}, -OR⁷, -SR⁷, -NO₂, -NR⁷R^{7'}, -NR⁷C(O)R^{7'}, and -NR⁷C(O)OR⁷, with R⁷ and R^{7'} as defined above for W.

2. A method of claim 1 wherein B of formula I is

- a) a substituted or unsubstituted bridged cyclic structure of up to 30 carbon atoms,
- b) a substituted or unsubstituted 6 member cyclic aryl moiety or a 5-6 member cyclic hetaryl moiety or
- c) a substituted or unsubstituted fused ring structure of from 2-3 fused aryl rings, hetaryl rings or both aryl and hetaryl rings.

3. A method as in claim 2 wherein B of formula I is a bridged cyclic structure of the formula -L-(ML¹)_q, where L is a 5 or 6 membered cyclic structure bound directly to D, L¹ comprises a substituted cyclic moiety having a least 5 members, M is a bridging group having at least one atom, q is an integer of from 1-3, and each cyclic structure of L and L¹ contains 0-4 members of the group consisting of nitrogen, oxygen and sulfur, wherein L¹ is substituted by at least one substituent selected from the group consisting of

$-\text{SO}_2\text{R}^a$, $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$ and $-\text{C}(\text{NR}^a)\text{R}^b$, wherein R^a and R^b are independently hydrogen or a carbon based moiety.

4. A method of claim 3 wherein M in the formula $-\text{L}-(\text{ML}^1)_q$, is selected from the group consisting of $-\text{O}-$, $-\text{S}-$, $-\text{N}(\text{R}^7)-$, $-(\text{CH}_2)_m-$, $-\text{C}(\text{O})-$, $-\text{CH}(\text{OH})-$, $-(\text{CH}_2)_m\text{O}-$, $-(\text{CH}_2)_m\text{S}-$, $-(\text{CH}_2)_m\text{N}(\text{R}^7)-$, $-\text{O}(\text{CH}_2)_m-$, $-\text{CHX}^a-$, $-\text{CX}^a_2-$, $-\text{S}-(\text{CH}_2)_m-$, $-\text{CR}^a\text{R}^b-$, and $-\text{N}(\text{R}^7)(\text{CH}_2)_m-$, where $m=1-3$, X^a is halogen, q is 1, and R^a and R^b are as defined in claim 3, and R^7 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{1-10} alkoxy, C_{2-10} alkenyl, C_{1-10} alkenoyl, up to per halosubstituted C_{1-10} alkyl, up to per halosubstituted C_{1-10} alkoxy, up to per halosubstituted C_{2-10} alkenyl and up to per halosubstituted C_{1-10} alkenoyl.

5. A method of claim 4 wherein L in the formula $-\text{L}-(\text{ML}^1)_q$ for B is a substituted 6 member cyclic aryl moiety, a substituted 5 or 6 member heterocyclic moiety, an unsubstituted 6 member cyclic aryl moiety, or an unsubstituted 5 or 6 member heterocyclic moiety, and L^1 in the formula $-\text{L}-(\text{ML}^1)_q$ for B, is a substituted aryl moiety having at least 6 cyclic members, an unsubstituted aryl moiety having at least 6 cyclic members, a substituted hetaryl moiety having at least 6 cyclic members or an unsubstituted hetaryl moiety having at least 6 cyclic members, said heterocyclic and hetaryl moieties having 1 to 4 members selected from the group of hetero atoms consisting of nitrogen, oxygen and sulfur with the balance of the hetaryl and heterocyclic moiety being carbon.

6. A method of claim 1 wherein B is phenyl, substituted phenyl, pyridinyl, substituted pyridinyl, pyrimidinyl, substituted pyrimidinyl, quinolinyl, substituted quinolinyl, isoquinolinyl, substituted isoquinolinyl or of the formula $-\text{L}(\text{ML}^1)_q$, wherein L^1 and L in formula $-\text{L}(\text{ML}^1)_q$ for B, are each independently selected from the group consisting of thiophene, substituted thiophene, phenyl, substituted phenyl, naphthyl, substituted naphthyl, pyridinyl, substituted pyridinyl, pyrimidinyl, substituted pyrimidinyl, quinolinyl, substituted quinolinyl, isoquinolinyl and substituted isoquinolinyl.

7. A method of claim 6 wherein B is a substituted group, substituted by -CN, halogen up to per halo, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, -OH, up to per halo substituted C₁₋₁₀ alkyl, up to per halo substituted C₁₋₁₀ alkoxy, -OR⁷, -SR⁷, -NR⁷R^{7'}, -CO₂R⁷, -C(O)NR⁷R^{7'}, -C(O)R⁷ or -NO₂, wherein each R⁷ and R^{7'} are independently selected from hydrogen, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, C₂₋₁₀ alkenyl, C₁₋₁₀ alkenoyl, up to per halosubstituted C₁₋₁₀ alkyl, up to per halosubstituted C₁₋₁₀ alkoxy, up to per halosubstituted C₂₋₁₀ alkenyl and up to per halosubstituted C₁₋₁₀ alkenoyl.

8. A compound of claim 6 wherein M in the formula -L-(ML¹) for B is -O-, -CH₂-, -S-, -NH-, -C(O)-, -O-CH₂- or -CH₂-O-.

9. A method of claim 6, wherein A has 1-3 substituents selected from the group consisting of C₁₋₁₀ alkyl, up to per halo substituted C₁₋₁₀ alkyl, -CN, -OH, halogen, C₁₋₁₀ alkoxy, up to per halo substituted C₁₋₁₀ alkoxy and C₃₋₁₀ heterocyclic moieties having at least 5 cyclic members and 1 to 2 heteroatoms selected from the group of consisting of nitrogen, oxygen and sulfur.

10. A method of claim 6 wherein L¹ is substituted 1 to 3 times by one or more substituents selected from the group consisting of -CN, halogen up to per halo, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, -OH, up to per halo substituted C₁₋₁₀ alkyl, up to per halo substituted C₁₋₁₀ alkoxy, -OR⁷, -SR⁷, -NR⁷R^{7'}, -CO₂R⁷, -C(O)NR⁷R^{7'}, -C(O)R⁷ or -NO₂, wherein each R⁷ and R^{7'} is independently selected from hydrogen, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, C₂₋₁₀ alkenyl, C₁₋₁₀ alkenoyl, up to per halosubstituted C₁₋₁₀ alkyl, up to per halosubstituted C₁₋₁₀ alkoxy, up to per halosubstituted C₂₋₁₀ alkenyl and up to per halosubstituted C₁₋₁₀ alkenoyl.

11. A method of claim 1 wherein a pharmaceutically acceptable salt of a compound of formula I is administered which is selected from the group consisting of

- a) basic salts of organic acids and inorganic acids selected from the group consisting of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric

acid, methanesulfonic acid, trifluorosulfonic acid, benzenesulfonic acid, p-toluene sulfonic acid (tosylate salt), 1-naphthalene sulfonic acid, 2-naphthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid; and

- b) acid salts of organic and inorganic bases containing cations selected from the group consisting of alkaline cations, alkaline earth cations, the ammonium cation, aliphatic substituted ammonium cations and aromatic substituted ammonium cations.

12. A method as in claim 1 for the treatment of a disease other than cancer.

13. A method as in claim 1 wherein the condition within a host treated by administering a compound of formula I is rheumatoid arthritis, osteoarthritis, septic arthritis, tumor metastasis, periodontal disease, corneal ulceration, proteinuria, coronary thrombosis from atherosclerotic plaque, aneurysmal aortic, birth control, dystrophic epidermolysis bullosa, degenerative cartilage loss following traumatic joint injury, osteopenias mediated by MMP activity, temporomandibular joint disease or demyelinating disease of the nervous system.

14. A method as in claim 1 wherein the condition within a host treated by administering a compound of formula I is rheumatic fever, bone resorption, postmenopausal osteoporosis, sepsis, gram negative sepsis, septic shock, endotoxic shock, toxic shock syndrome, systemic inflammatory response syndrome, inflammatory bowel disease (Crohn's disease and ulcerative colitis), Jarisch-Herxheimer reaction, asthma, adult respiratory distress syndrome, acute pulmonary fibrotic disease, pulmonary sarcoidosis, allergic respiratory disease, silicosis, coal worker's pneumoconiosis, alveolar injury, hepatic failure, liver disease during acute inflammation, severe alcoholic hepatitis, malaria (*Plasmodium falciparum* malaria and cerebral malaria), ~~non-insulin-dependent~~ diabetes mellitus (NIDDM), congestive heart failure, damage following heart disease, atherosclerosis, Alzheimer's disease, acute encephalitis, brain injury, multiple sclerosis

(demyelation and oligiodendrocyte loss in multiple sclerosis), advanced cancer, lymphoid malignancy, pancreatitis, impaired wound healing in infection, inflammation and cancer, myelodysplastic syndromes, systemic lupus erythematosus, biliary cirrhosis, bowel necrosis, psoriasis, radiation injury/ toxicity following administration of monoclonal antibodies, host-versus-graft reaction (ischemia reperfusion injury and allograft rejections of kidney, liver, heart, and skin), lung allograft rejection (obliterative bronchitis) or complications due to total hip replacement.

15. A method as in claim 1 wherein the condition within a host treated by administering a compound of formula I is an infectious disease selected from the group consisting of tuberculosis, Helicobacter pylori infection during peptic ulcer disease, Chaga's disease resulting from Trypanosoma cruzi infection, effects of Shiga-like toxin resulting from E. coli infection, effects of enterotoxin A resulting from Staphylococcus infection, meningococcal infection, and infections from Borrelia burgdorferi, Treponema pallidum, cytomegalovirus, influenza virus, Theiler's encephalomyelitis virus, and the human immunodeficiency virus (HIV).

16. A method as in claim 3 wherein:

R_a and R_b are,

a) independently hydrogen,

a carbon based moiety selected from the group consisting of C₁-C₁₀ alkyl, C₁-C₁₀ alkoxy, C₃₋₁₀ cycloalkyl having 0-3 hetero atoms selected from N, S and O, C₂₋₁₀ alkenyl, C₁₋₁₀ alkenoyl, C₆₋₁₄ aryl, C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from O, N and S, C₇₋₂₄ aralkyl, C_{7-C24} alkaryl, substituted C₁₋₁₀ alkyl, substituted C₁₋₁₀ alkoxy, substituted C₃₋₁₀ cycloalkyl having 0-3 heteroatoms selected from N, S and O, substituted C₆₋₁₄ aryl, substituted C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, S and O, substituted C₇₋₂₄ aralkyl, substituted C₇₋₂₄ alkaryl, where R_a and R_b are a substituted group, they are substituted by halogen up to per halo, hydroxy, C₁₋₁₀ alkyl, C₃₋₁₂ cycloalkyl having 0-3 heteroatoms selected from O, S and N, C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, S and O, C₁₋₁₀ alkoxy, C₆₋₁₂ aryl, C₁₋₆ halo substituted alkyl up to per halo alkyl, C_{6-C12} halo substituted aryl up to per halo aryl, C_{3-C12} halo substituted cycloalkyl having

0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C₃-C₁₂ hetaryl up to per halo heteraryl, halo substituted C₇-C₂₄ aralkyl up to per halo aralkyl, halo substituted C₇-C₂₄ alkaryl up to per halo alkaryl, and -C(O)R_g; or

-OSi(R_f)₃ where R_f is hydrogen, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkyl having 0-3 heteroatoms selected from O, S and N, C₆₋₁₂ aryl, C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from O, S and N, C₇₋₂₄ aralkyl, substituted C₁₋₁₀ alkyl, substituted C₁₋₁₀ alkoxy, substituted C₃₋₁₂ cycloalkyl having 0-3 heteroatoms selected from O, S and N, substituted C₃₋₁₂ heteraryl having 1-3 heteroatoms selected from O, S, and N, substituted C₆₋₁₂ aryl, and substituted C₇₋₂₄ alkaryl, where R_f is a substituted group it is substituted halogen up to per halo, hydroxy, C₁₋₁₀ alkyl, C₃₋₁₂ cycloalkyl having 0-3 heteroatoms selected from O, S and N, C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, S and O, C₁₋₁₀ alkoxy, C₆₋₁₂ aryl, C₇₋₂₄ alkaryl, C₇₋₂₄ aralkyl, C₁₋₆ halo substituted alkyl up to per halo alkyl, C₆₋₁₂ halo substituted aryl up to per halo aryl, C₃₋₁₂ halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C₃₋₁₂ hetaryl up to per halo heteraryl, halo substituted C₇₋₂₄ aralkyl up to per halo aralkyl, halo substituted C₇₋₂₄ alkaryl up to per halo alkaryl, and -C(O)R_g.

or

b) R_a and R_b together form a 5-7 member heterocyclic structure of 1-3

heteroatoms selected from N, S and O, or a substituted 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O with substituents selected from the group consisting of halogen up to per halo, hydroxy, C₁₋₁₀ alkyl, C₃₋₁₂ cycloalkyl having 0-3 heteroatoms selected from O, S and N, C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, S and O, C₁₋₁₀ alkoxy, C₆₋₁₂ aryl, C₇₋₂₄ alkaryl, C₇₋₂₄ aralkyl, halo substituted C₁₋₆ alkyl up to per halo alkyl, halo substituted C₆₋₁₂ aryl up to per halo aryl, halo substituted C₃₋₁₂ cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C₃₋₁₂ hetaryl up to per halo heteraryl, halo substituted C₇₋₁₂ aralkyl up to per halo aralkyl, halo substituted C₇₋₂₄ alkaryl up to per halo alkaryl, and -C(O)R_g.

or

c) one of R_a or R_b is $-C(O)-$, a C_1-C_5 divalent alkylene group or a substituted C_1-C_5 divalent alkylene group bound to the moiety L to form a cyclic structure with at least 5 members,

wherein the substituents of the substituted C_1-C_5 divalent alkylene group are selected from the group consisting of halogen, hydroxy, C_{1-10} alkyl, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, C_{1-10} alkoxy, C_{6-12} aryl, C_7-C_{24} alkaryl, C_7-C_{24} aralkyl, C_{1-6} halo substituted alkyl up to per halo alkyl, C_6-C_{12} halo substituted aryl up to per halo aryl, C_3-C_{12} halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C_3-C_{12} hetaryl up to per halo heteraryl, halo substituted C_7-C_{24} aralkyl up to per halo aralkyl, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, and $-C(O)R_g$,

where R_g is C_{1-10} alkyl; $-CN$, $-CO_2R_d$, $-OR_d$, $-SR_d$, $-NO_2$, $-C(O)R_e$, $-NR_dR_e$, $-NR_dC(O)OR_e$ and $-NR_dC(O)R_e$, and R_d and R_e are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkyl having 0-3 heteroatoms selected from O, N and S, C_{6-12} aryl, C_3-C_{12} hetaryl with 1-3 heteroatoms selected from O, N and S and C_7-C_{24} aralkyl, C_7-C_{24} alkaryl, up to per halo substituted C_1-C_{10} alkyl, up to per halo substituted C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, N and S, up to per halo substituted C_6-C_{14} aryl, up to per halo substituted C_3-C_{12} hetaryl having 1-3 heteroatoms selected from O, N, and S, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, and up to per halo substituted C_7-C_{24} aralkyl.

17. A method as in claim 4, wherein said substituted cyclic moiety L^1 is phenyl, pyridyl or pyrimidinyl.

18. A method of claim 3 wherein L^1 is substituted by $-C(O)NR^aR^b$ or $-SO_2NR^aR^b$.

19. A method for the treatment of a disease mediated by p38 kinase other than cancer which comprises administering a compound selected from the group consisting of

N-(2-Methoxy-3-quinolyl)-*N'*-(4-[3-(*N*-methylcarbamoyl)phenoxy]phenyl)urea

N-(2-Methoxy-3-quinolyl)-*N'*-(4-[2-(*N*-methylcarbamoyl)-4-pyridyloxy]phenyl)urea

N-(2-Methoxy-3-quinolyl)-*N'*-(4-(2-carbamoyl-4-pyridyloxy)phenyl)urea

N-(2-Methoxy-3-quinolyl)-*N'*-(3-[2-(*N*-methylcarbamoyl)-4-pyridyloxy]phenyl)urea

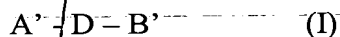
N-(2-Methoxy-3-quinolyl)-*N'*-(3-(2-carbamoyl)-4-pyridyloxy)phenyl)urea

N-(2-Methoxy-3-quinolyl)-*N'*-(4-[3-(*N*-isopropylcarbamoyl)phenoxy]phenyl)urea

N-(2-Methoxy-3-quinolyl)-*N'*-(4-[4-methoxy-3-(*N*-methylcarbamoyl)phenoxy]phenyl)urea

N-(3-Isoquinolyl)-*N'*-(4-[2-(*N*-methylcarbamoyl)-4-pyridyloxy]phenyl)urea
and pharmaceutically acceptable salts thereof.

20. A compound of the following formula



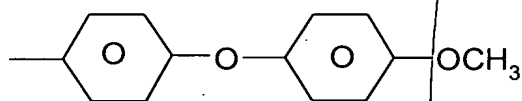
or a pharmaceutically acceptable salt thereof, wherein

D is -NH-C(O)-NH-,

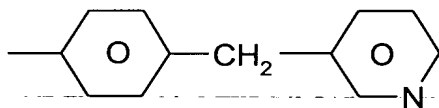
A' is selected from the group consisting of substituted t-butylpyridinyl, unsubstituted t-butylpyridyl, substituted (trifluoromethyl)pyridyl, unsubstituted (trifluoromethyl)pyridyl, substituted isopropylpyridyl, unsubstituted isopropylpyridyl, substituted (2-methyl-2-butyl)pyridyl, unsubstituted (2-methyl-2-butyl)pyridyl, substituted (3-ethyl-3-pentyl)pyridyl, unsubstituted (3-ethyl-3-pentyl)pyridyl, substituted isoquinolinyl, unsubstituted isoquinolinyl and unsubstituted quinolinyl,

B' is

- a) a substituted or unsubstituted aryl ring having 6 cyclic members,
- b) a substituted or unsubstituted heterocyclic, ring having at least 5 cyclic members and 1-3 heteroatoms selected from O, S and N,
- c) a substituted or unsubstituted fused ring structure of from 2-3 fused aryl rings, hetaryl rings or both aryl or hetaryl rings of up to 30 carbon atoms or



where A' is substituted or unsubstituted t-butylpyridyl (trifluoromethyl)pyridyl, isopropylpyridyl, (2-methyl-2-butyl)pyridyl or (3-ethyl-3-pentyl)pyridyl, or



where A' is substituted isoquinolinyl, unsubstituted isoquinolinyl or unsubstituted quinolinyl.

21. A pharmaceutical composition comprising a compound of claim 20 and a physiologically acceptable carrier.

22. A compound of claim 20, wherein A' has 1-3 substituents selected from the group consisting of C₁₋₁₀ alkyl, up to per halo substituted C₁₋₁₀ alkyl, -CN, -OH, halogen, C₁₋₁₀ alkoxy, up to per halo substituted C₁₋₁₀ alkoxy and C₃₋₁₀ heterocyclic moieties having at least a five cyclic members and 1 to 2 heteroatoms selected from the group of consisting of nitrogen, oxygen and sulfur.

23. A compound of claim 20 wherein B' is a substituted group substituted by -CN, halogen, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, -OH, up to per halo substituted C₁₋₁₀ alkyl, up to per halo substituted C₁₋₁₀ alkoxy -OR⁷, -SR⁷, -NR⁷R^{7'}, -NR⁷C(O)OR^{7'}, -NR⁷C(O)R^{7'} or -NO₂, wherein each R⁷ and R^{7'} is independently selected from hydrogen, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, C₂₋₁₀ alkenyl, C₁₋₁₀ alkenoyl, up to per halosubstituted C₁₋₁₀ alkyl, up to per halosubstituted C₁₋₁₀ alkoxy, up to per halosubstituted C₂₋₁₀ alkenyl and up to per halosubstituted C₁₋₁₀ alkenoyl.

24. A compound of claim 20 wherein B' is thiophene, substituted thiophene, substituted phenyl, substituted phenyl, pyridinyl, substituted pyridinyl, pyrimidinyl, substituted pyrimidinyl, quinolinyl, substituted quinolinyl, isoquinolinyl, substituted isoquinolinyl, naphthyl or substituted naphthyl.

25. A compound of claim 20 which is a pharmaceutically acceptable salt of a compound of formula I' selected from the group consisting of

- a) basic salts of organic acids and inorganic acids selected from the group consisting of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, trifluorosulfonic acid, benzenesulfonic acid, p-toluene sulfonic acid (tosylate salt), 1-naphthalene sulfonic acid, 2-naphthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid; and
- b) acid salts of organic and inorganic bases containing cations selected from the group consisting of alkaline cations, alkaline earth cations, the ammonium cation, aliphatic substituted ammonium cations and aromatic substituted ammonium cations.

26. A compound selected from the group consisting of

N-(4-tert-butylpyridinyl)-N'-(4-methylphenyl) urea

N-(4-tert-butylpyridinyl)-N'-(4-fluorophenyl) urea

N-(4-tert-butylpyridinyl)-N'-(2,3-dichlorophenyl) urea
 N-(4-tert-butylpyridinyl)-N'-(1-naphthyl) urea
 N-(4-tert-butylpyridinyl)-N'-(4-4-methoxyphenoxy)phenyl) urea
 N-(2-)(5-trifluoromethyl)pyridinloxy-N'-(4-4-pyridylmethyl)phenyl) urea
 N-(2-)(5-trifluoromethyl)pyridinloxy-N'-(3-4-pyridylthio)phenyl) urea
 N-(3-isoquinolyl)-N'-(4-methylphenyl) urea
 N-(3-isoquinolyl)-N'-(4-fluorophenyl) urea
 N-(3-isoquinolyl)-N'-(2,3-dichlorophenyl) urea
 N-(3-isoquinolyl)-N'-(1-naphthyl) urea
 N-(3-isoquinolyl)-N'-(4-4-pyridinylmethyl)phenyl) urea
 N-(3-quinolyl)-N'-(4-4-pyridinylmethyl)phenyl) urea

27. A method of treating a disease mediated by p38 within a host, said method comprising administering a compound of claim 20.

28. A pharmaceutical composition for the treatment of a disease within a host mediated by p38 comprising an amount of a compound of Formula I effective to inhibit p38 mediated events,

A - D - B (I)

or a pharmaceutically acceptable salt thereof, in an amount effective to treat a disease mediated by p38 and a physiologically acceptable carrier:

wherein

D is -NH-C(O)-NH- ,

A is as defined in claim 1

B is as defined in claim 1

29. A pharmaceutical composition as in claim 28 wherein B of formula I is

- a) a substituted or unsubstituted bridged cyclic structure of up to 30 carbon atoms,
- b) a substituted or unsubstituted 6 member cyclic aryl moiety or a 5-6 member cyclic hetaryl moiety or
- c) a substituted or unsubstituted fused ring structure of from 2-3 fused aryl rings, hetaryl rings or both aryl and hetaryl rings.

30. A pharmaceutical composition as in claim 29 wherein B of formula I is a bridged cyclic structure of the formula $-L-(ML^1)_q$, where L is a 5 or 6 membered cyclic structure bound directly to D, L^1 comprises a substituted cyclic moiety having a least 5 members, M is a bridging group having at least one atom, q is an integer of from 1-3, and each cyclic structure of L and L^1 contains 0-4 members of the group consisting of nitrogen, oxygen and sulfur, wherein L^1 is substituted by at least one substituent selected from the group consisting of $-SO_2R_x$, $-C(O)R_x$, and $-C(NR_y)R_z$ wherein R_y is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally halosubstituted, up to per halo,

R_z is hydrogen or a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

R_x is R_z or NR_aR_b where R_a and R_b are

- a) independently hydrogen,

a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen, or

$-OSi(R_f)_3$ where R_f is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms,

which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

- b) R_a and R_b together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, or a substituted 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O substituted by halogen, hydroxy or carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or
- c) one of R_a or R_b is $-C(O)-$, a C_1-C_5 divalent alkylene group or a substituted C_1-C_5 divalent alkylene group bound to the moiety L to form a cyclic structure with at least 5 members, wherein the substituents of the substituted C_1-C_5 divalent alkylene group are selected from the group consisting of halogen, hydroxy, and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen.

31. A pharmaceutical composition as in claim 30 wherein the cyclic structures of B and L bound directly to D are not substituted in the ortho position by $-OH$ or a moiety having an ionizable hydrogen and a pK_a of 10 or less.

32. A pharmaceutical composition as in claim 28 wherein B of Formula I is a substituted or unsubstituted six member aryl moiety or at least a five member heterocyclic moiety, said heterocyclic moiety having 1 to 4 members selected from the group of heteroatoms consisting of nitrogen, oxygen and sulphur with the balance of the heterocyclic moiety being carbon.

33. A pharmaceutical composition as in claim 30 wherein B of Formula I is an unsubstituted phenyl group, an unsubstituted pyridyl group, an unsubstituted pyrimidinyl group, a phenyl group substituted by a substituent selected from the group consisting of halogen and W_n wherein W and n are as defined in claim 30, a pyrimidinyl group substituted by a substituent selected from halogen and W_n , wherein W and n are as defined in Claim 30, or a pyridyl group substituted by a substituent selected from the group consisting of halogen and W_n wherein W and n are as defined in claim 30.

34. A pharmaceutical composition as in claim 30, wherein L, the 5 or 6 member cyclic structure bound directly to D, is a substituted or unsubstituted 6 member heteroaryl moiety, wherein said heteroaryl moiety has 1 to 4 members selected from the group of heteroatoms consisting of nitrogen, oxygen and sulphur with the balance of said heteroaryl moiety being carbon, wherein the one or more substituents are selected from the group consisting of halogen and W_n, wherein W and n are as defined in claim 30.

35. A pharmaceutical composition as in claim 30, wherein L, the 5 or 6 member cyclic structure bound directly to D, is a substituted phenyl, substituted thiophene, unsubstituted thiophene, substituted naphthyl, unsubstituted naphthyl, unsubstituted phenyl, substituted pyridyl, unsubstituted pyridyl group, unsubstituted pyrimidinyl or substituted pyrimidinyl.

36. A pharmaceutical composition as in claim 30, wherein said substituted cyclic moiety L¹ is phenyl, pyridyl or pyrimidinyl and M is one or more bridging groups selected from the group consisting of -O-, -S-, -N(R⁷)-, -(CH₂)_m-, -C(O)-, -CH(OH)-, -(CH₂)_mO-, -(CH₂)_mS-, -(CH₂)_mN(R⁷)-, -O(CH₂)_m- CHX^a-, -CX^a₂-, -S-(CH₂)_m- and -N(R⁷)(CH₂)_m-, where m= 1-3, X^a is halogen and R⁷ is hydrogen or a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen up to per halo.

37. A pharmaceutical composition as in claim 30 wherein L¹ is substituted by -C(O)R_x.

38. A pharmaceutical composition as in claim 30 wherein L¹ is substituted by -C(O)R_x or -SO₂R_x, wherein R_x is NR_aR_b.

39. A pharmaceutical composition for the treatment of a disease within a host mediated by p38 comprising a compound selected from the group consisting of

N-(2-Methoxy-3-quinolyl)-*N'*-(4-[3-(*N*-methylcarbamoyl)phenoxy]phenyl)urea,

N-(2-Methoxy-3-quinolyl)-*N'*-(4-[2-(*N*-methylcarbamoyl)-4-pyridyloxy]phenyl)urea,

N-(2-Methoxy-3-quinolyl)-*N'*-(4-(2-carbamoyl-4-pyridyloxy)phenyl)urea,

N-(2-Methoxy-3-quinolyl)-*N'*-(3-[2-(*N*-methylearbamoyl)-4-pyridyloxy]phenyl)urea,

N-(2-Methoxy-3-quinolyl)-*N'*-(3-(2-carbamoyl)-4-pyridyloxy)phenyl)urea ,

N-(2-Methoxy-3-quinolyl)-*N'*-(4-[3-(*N*-isopropylcarbamoyl)phenoxy]phenyl)urea,

N-(2-Methoxy-3-quinolyl)-*N*'-(4-[4-methoxy-3-(*N*-methylcarbamoyl)phenoxy]phenyl)urea,

N-(3-Isoquinolyl)-*N*¹-(4-[2-(*N*-methylcarbamoyl)-4-pyridyloxy]phenyl)urea
and pharmaceutically acceptable salts thereof.

4/4/03

92

BAYER 14